The optimal treatment of stage I nonsmall cell lung cancer in the era of SABR and modern day lung resections

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Both SABR and surgical resection may have a role to play in the treatment of clinical stage I NSCLC, and future studies should focus on the biology of these mostly curable lung cancers to minimise under-and overtreating patients https://bit.ly/2BMlsWm

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The investigators of the SABRTooth trial must be congratulated for completing this randomised controlled feasibility study aiming to address the treatment of peripheral clinical stage I nonsmall cell lung cancer (NSCLC) in patients deemed at higher risks from surgery [1]. The five-centre National Health Service study was well designed and built on the strengths and weaknesses of the previously prematurely closed ROSEL and STARS trials. In addition, by design, the study allowed for modifications in recruitment strategies per their own successes and failures as data was accumulating during the 18 months accrual period. Despite these schemes to optimise recruitment, the primary goal of recruiting three patients per month was never reached and, as seen in previous attempts in the Netherlands and the USA, SABRTooth demonstrated that a randomised trial comparing surgery and stereotactic ablative radiotherapy (SABR) in the treatment of these patients is not feasible in the UK: patients' preferences for one approach or the other, a possible lack of equipoise by the research team members presenting the options to the patients and patients not being comfortable with a "flip of the coin" deciding which radically different treatment they may receive were all seen as major obstacles to better accrual. As noted in the manuscript, other trials attempting to compare surgery and SABR in the treatment of early stage NSCLC have incorporated modified accrual schemes and are ongoing.

Even if such trials were feasible, one could question whether any study comparing the two strategies would be powered enough to clearly address the debate. The same conundrum affects trials comparing wedge resections to anatomical resections for the treatment of solid peripheral stage I NSCLC, based on the following observations. A proportion of patients with clinical stage I disease can be treated with a simple surgical wedge resection (non-anatomical) (or SABR) and will be cured. At the extreme opposite, a proportion of the clinical stage I patients could be treated by a lobectomy with radical lymphadenectomy, but they will declare their stage IV disease after surgery and likely succumb to their cancer. In neither of these 2 groups, does lymphatic drainage resection have any therapeutic impact on the survival or lack thereof. In between these 2 populations however, there is a group of clinical stage I patients in whom a field resection of the draining lymphatics may be therapeutic and in whom an anatomical resection will be curative where a wedge resection would not, and for that matter neither would SABR. The proportion of

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such patients is probably relatively small though likely rises as the size of the tumours increases. As a result, trials addressing the treatment of clinical stage I patients will probably always be underpowered to be able to see the differences.

It is interesting to note that the same stage I population "at risk" should also benefit from adjuvant systemic therapy though, to date, most trials have not been able to demonstrate such benefit after resection of stage I disease, possibly for the "statistical" reasons described above. Relying solely on the TNM descriptors to determine the need for adjuvant therapy is insufficient and efforts are underway to identify additional tools that could help us determine who needs additional help and who does not.

To explain reported survivals after SABR that are as good as seen with surgery in non-randomised populations, the literature mentions a possible but controversial abscopal effect with SABR that potentially addresses the lymphatic involvement. To me, the main issue is that most of these reports describe survivals at 3 years, a follow-up that is far too short when analysing any treatment for stage I disease. One has to remember that it took 4 years for the survival curves to come apart in the LCSG 821 trial that compared lobectomies to less in the treatment of stage I disease in the early 1980s, in a period where biologically NSCLC was probably more aggressive, as low grade peripheral adenocarcinomas were few and far between then.

The observations noted above point towards a need for the concept of "personalised treatment" of stage I NSCLC where, beyond size and tumour location, as well as computed tomography (CT) and CT-positron emission tomography plain radiological characteristics, one could interrogate the tumour to determine its best treatment course, be it through SABR, a wedge resection or an anatomical surgical resection. Whether one could rely on genomics or proteomics profiles from the tumour biopsy, or even from circulating tumour DNA, or possibly radiomics or a combination thereof, are all interesting possibilities to explore. Both SABR and surgical resection have a role to play in the treatment of clinical stage I NSCLC and it may not be that one is better than the other in all instances. Future efforts to address the treatment of these patients should focus on the biology of these mostly curable lung cancers so that we minimise undertreating as well as overtreating these cancers.

Conflict of interest: E. Vallieres reports personal fees for lectures from AstraZeneca, personal fees for advisory board work from Regeneron, AbbVie and Oncocyte, personal fees for consultancy from Olympus, outside the submitted work.

References

1 Franks KN, McParland L, Webster J, *et al.* SABRTooth: a randomised controlled feasibility study of stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I nonsmall cell lung cancer considered to be at higher risk of complications from surgical resection. *Eur Respir J* 2020; 56: 2000118.